Volumetric upper airway changes after rapid maxillary expansion: a systematic review and meta-analysis

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Abstract: BACKGROUND Although Rapid Maxillary Expansion (RME) has been used for over a century, its effect on upper airways has not yet adequately been assessed in an evidence-based manner. OBJECTIVE To investigate the volumetric changes in the upper airway spaces following RME in growing subjects by means of acoustic rhinometry, three-dimensional radiography and digital photogrammetry. SEARCH METHODS Literature search of electronic databases and additional manual searches up to February 2016. SELECTION CRITERIA Randomized clinical trials, prospective or retrospective controlled clinical trials and cohort clinical studies of at least eight patients, where the RME appliance was left in place for retention, and a maximum follow-up of 8 months post-expansion. DATA COLLECTION AND ANALYSIS After duplicate data extraction and assessment of the risk of bias, the mean differences and 95 per cent confidence intervals (CIs) of upper airway volume changes were calculated with random-effects meta-analyses, followed by subgroup analyses, meta-regressions, and sensitivity analyses. RESULTS Twenty studies were eligible for qualitative synthesis, of which 17 (3 controlled clinical studies and 14 cohort studies) were used in quantitative analysis. As far as total airway volume is concerned patients treated with RME showed a significant increase post-expansion (5 studies; increase from baseline: 1218.3mm(3); 95 per cent CI: 702.0 to 1734.6mm(3)), which did not seem to considerably diminish after the retention period (11 studies; increase from baseline: 1143.9mm(3); 95 per cent CI: 696.9 to 1590.9mm(3)). LIMITATIONS However, the overall quality of evidence was judged as very low, due to methodological limitations of the included studies, absence of untreated control groups, and inconsistency among studies. CONCLUSIONS RME seems to be associated with an increase in the nasal cavity volume in the short and in the long term. However, additional well-conducted prospective controlled clinical studies are needed to confirm the present findings. REGISTRATION None. FUNDING Australian Society of Orthodontics Foundation for Research and Education Inc.

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Title Page

Volumetric Upper Airway Changes after Rapid Maxillary Expansion: A Systematic Review and Meta-Analysis

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Volumetric upper airway changes after rapid maxillary expansion: a systematic review and meta-analysis

Summary

Objective: To investigate the volumetric changes in the upper airway spaces following Rapid Maxillary Expansion (RME) in growing subjects by means of acoustic rhinometry, three-dimensional radiography and digital photogrammetry.

Search methods: Literature search of electronic databases and additional manual searches up to February 2016.

Selection criteria: Randomized clinical trials, prospective or retrospective controlled clinical trials and cohort clinical studies of at least eight patients, where the RME appliance was left in place for retention, and a maximum follow-up of 8 months post-expansion.

Data collection and analysis: After duplicate data extraction and assessment of the risk of bias, the mean differences (MDs) and 95% confidence intervals (CIs) of upper airway volume changes were calculated with random-effects meta-analyses, followed by subgroup analyses, meta-regressions, and sensitivity analyses.

Results: Twenty studies were eligible for qualitative synthesis, of which 17 (3 controlled clinical studies and 14 cohort studies) were used in quantitative analysis. As far as total airway volume is concerned patients treated with RME showed a significant increase both post-expansion (5 studies; increase from baseline: 1218.3 mm^3; 95% CI: 702.0 to 1734.6 mm^3), which did not seem to considerably diminish after the retention period (11 studies; increase from baseline: 1143.9 mm^3; 95% CI: 696.9 to 1590.9 mm^3). However, the overall quality of evidence was judged as very low, due to methodological limitations of the included studies, absence of untreated control groups, and inconsistency among studies.

Conclusions: RME seems to be associated with an increase in the nasal cavity volume in the short- and in the long-term. However, additional well-conducted prospective controlled clinical studies are needed to confirm the present findings.

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Introduction

Rationale

Maxillary expansion as an orthodontic treatment modality has been reported since the 1860's (1). Rapid Maxillary Expansion (RME) aims to resolve maxillary transverse deficiencies, correct posterior dental crossbites, create arch space for relief of crowding, prevent maxillary canine impaction, and reduce nocturnal enuresis (2-4). Separation of the maxillary halves extends directly to the nasal cavity through lateral separation of the nasal walls and lowering of the palatal vault (5). Reported benefits to the upper airway include improving allergic rhinitis, asthma, and recurrent ear or nasal infections (6). Many researchers have suggested that RME is a successful means of increasing the nasal permeability and reducing airway resistance, based on both objective and subjective evidence (7, 8). Reduced airway resistance reduces negative pressure during ventilation, with promising results of RME shown in the treatment of paediatric sleep disordered breathing, including obstructive sleep apnoea (9). The effects on more distant structures include stretching of the tensor palatine muscles by the expanding maxilla with subsequent improvement in drainage of the Eustachian tubes, aiding in reducing otitis media and conductive hearing loss (10). Enlarged palatal space may also allow for an improved tongue posture, which could facilitate increased airway space in the oropharynx (11).

Decreased airflow can be observed in various parts of the upper airways. In cases of considerable obstruction to the nasal airflow, the respiratory pattern can shift towards mouth breathing, although breathing mode cannot be robustly predicted by nasal resistance data alone (8). On the other side some researchers suggest that reduced nasal volumes are associated with mouth breathing (12). The interrelationship between respiratory obstruction, malocclusion, and facial growth continues to be debated after nearly a century of controversy (13). Interest in this subject has been rekindled in the past decades, based on the possible role of craniofacial morphology, and especially the shape/ dimension of the upper airways, on obstructive sleep apnoea (14).

Many studies have assessed linear transverse dental and skeletal changes produced by maxillary expansion, but these changes do not necessarily reflect airway dimension changes (15, 16). Previous reports indicate that maxillary expansion is associated with an increase in nasal width, cross-sectional area, and volume (5, 17, 18). Subjective improvement in nasal breathing has also been considered as a concomitant result (7, 8). However, evidence on the changes induced by RME on upper airway volumes further from the nasal cavity, particularly the pharynx, is still inconclusive.

Accurate quantification of RME-induced changes at the upper airways has been a challenge. Linear measurements as performed on cephalograms cannot accurately express the upper airways (19). On the other side, the dimensional accuracy of both conventional computed tomography (CT) and cone-beam computed tomography (CBCT) in quantifying the volume of the upper airway has long been verified (14, 20) with small method error, even though imaging reproducibility of dynamic regions has been suggested to be inconsistent (21). Although CBCT can offer reduced cost and radiation exposure to the patient compared to traditional CT, the latter shows reduced image noise, improved contrast resolution and accuracy to distinguish between soft tissues and air spaces over the former (22).

Acoustic Rhinometry (AR), developed by Hilberg (23) can be used to objectively evaluate the nasal anatomy based on the reflection of sound waves within the nasal cavity. Measurements are then processed to calculate nasal cavity area, volume, and resistance (15). Use of a decongestant is common to produce readings that are minimally influenced by the highly dynamic nasal mucosal tissues (24). Although AR has been shown to have good agreement with magnetic resonance imaging and CT in the anterior nasal cavity up to 6 cm from the nostrils (25), it may over-estimate cross sectional areas in the posterior portion of the nasal cavity and pharynx, due to partial contribution of the maxillary sinuses (26).

Objectives

A previous systematic review (27) reported on the subject, however, only studies up to 2010 were included, no meta-analysis was performed, and the quality of overall evidence was not assessed with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (28). The aim of this study was to summarize in a systematic manner evidence on upper airway volume changes induced by RME based on clinical studies in growing patients.

Materials and Methods

Protocol and Registration

The protocol of the present systematic review was based *a priori* on Cochrane Handbook for Systematic reviews of Interventions 5.1.0. (29). Reporting of this Systematic Review follows the PRISMA statement (30), its extension for abstracts (31), and was not registered.

Information Sources and Search

Systematic search of major electronic databases was conducted covering publications in English from inception of each database through February 1st, 2016. Electronic searches were performed in Medline via Ovid (1965 to 1st February 2016), PREMEDLINE (all available), Old Medline (1946 to 1965), Embase (1947 to 1st February 2016), Cochrane Central Register of Controlled Trials (CENTRAL). Unpublished literature was searched electronically through ClinicalTrials.gov (www.clinicaltrials.gov) and ISRCTN registry (http://www.isrctn.com/) using the terms "expansion", "airway" and "volume" without any limitations to publication date. Additional hand searching of reference lists of relevant articles, grey literature in Google Scholar, and correspondence with experts in the field was conducted for location of any additional studies. The search keywords and strategy were developed in consultation with a senior health sciences librarian and the search was performed independently by two authors (LB and OD). Exact search strategies for MEDLINE via Ovid and Embase are shown in Supplementary Tables 1 and 2, respectively.

Eligibility Criteria

The eligibility criteria of included studies were determined *a priori* (Supplementary Table 3) with the scope of evaluating RME-induced volumetric changes in any region of the upper airway, made with any diagnostic modality. Eligible studies should report both baseline and post-expansion data. In order to minimize the confounding factor of relapse on the immediate volumetric airway changes, it was decided to include only time-points either immediately following the active expansion period or immediately after the retention period (to a maximum of 8 months of retention). Data from follow-up records taken after further non-retained periods, after a subsequent orthodontic treatment phase or at long-term reviews were not used in order to avoid confounding. Only studies on growing patients (using the cut-off age of 18 years) were included, as skeletal changes produced by RME in this period are more consistent. Due to the scarcity of existing studies, we included randomized and non-randomized controlled clinical trials and non-randomized cohort clinical studies that included at least 8 patients.

Study selection and Data Collection

Study selection and data collection was conducted by two independent blinded authors (LB and OD), with discrepancies being resolved by discussion with the last author (AKP). Title and abstract screening was performed

blinded (32) by these two authors by grading studies as “yes”, “no” or “maybe” based on the information provided by the title and abstract. Full-text was located for all articles graded with “‘yes” or “maybe”, as well as studies where no abstract was available, or the information available was inconclusive in reaching a decision. The inclusion and exclusion criteria were rigorously applied to the full-text articles and where questions remained, efforts were made to contact the authors of the study for.

Data collection was performed from the same two blinded authors using a customized data extraction form (Supplementary Table 4). The primary outcome measure sought was volumetric changes in any region of the upper airway. The upper airway was defined as including the nose, nasal passages, paranasal sinuses, oral cavity, pharynx (nasopharynx, oropharynx, hypopharynx) (33) and the portion of the larynx above the vocal cords (34). Information related to the study samples including sample size, age, gender, as well as patient selection criteria were recorded. Details of the type of RME device utilized as well as specifics of the expansion protocol, timing, turning frequency, amount of activation, and retention were retrieved from all included studies. The modality and technique used to quantify the airway volume, as well as the exact time-points that these were recorded were extracted. Measurements were accepted from 3 specific time-points only, defined as: T1, immediately prior to insertion of RME appliance; T2, immediately at completion of the active expansion phase; and T3, immediately at completion of the retention phase (maximum 8 months).

Risk of bias within individual studies

The Cochrane Collaboration’s risk of bias tool (35) was used to assess the internal validity of included randomized controlled trials. The methodological adequacy of included non-randomized trials was assessed with a customized tool that was developed especially for this systematic review based on various appraisal tools (including the Newcastle-Ottawa scale) and empirical evidence of bias in orthodontic clinical research (Supplementary Table 5) (36-42). The developed checklist comprised 15 individual questions pertaining to four domains: study design, study conduct, statistical analysis, and conclusions, with a maximum score of 25. Studies were graded descriptively as having overall high (score > 20), moderate ($20 \leq$ score ≤ 13) or low (score < 13) methodological adequacy. However, specific domain questions were also used to determine the strength of the evidence, when drawing conclusions from the final data.

Summary Measures

The primary outcome of this systematic review was the overall upper airway volume, as this is the most clinically relevant outcome for the patient. As mentioned above, results from all diagnostic modalities (including AR, CT, etc.) were included, but were analyzed separately. All results were calculated as increment final (post-expansion or post-retention) minus initial (pre-expansion) upper airway volume. As many studies reported on the volume of various parts of the upper airway, we pooled for each study the total airway volume that was reported. As a secondary outcome, we adopted the changes in the volume of each upper airway volume separately and we calculated the RME-induced change likewise. For both primary and secondary outcomes, main emphasis was given on the results of controlled clinical trials, as these have greater internal validity. Results of uncontrolled cohort studies were also reported in order to provide a quantitative overview of the effects of RME on upper airway volume, but were interpreted with caution.

Data Synthesis

As the effects of RME were expected to vary among the included studies according to the different treatment protocols, RME appliances, patient characteristics, airway regions, and measurements techniques, a random-effects model according to DerSimonian and Laird (43) was judged appropriate to encompass this variability (44). For all meta-analyses the Mean Differences (MDs) and the associated 95% Confidence Intervals (CIs) were calculated. Forest plots were constructed to depict the meta-analysis results and were augmented with contours denoting the magnitude of the observed effects.

Between-trial heterogeneity was quantified with the I^2 statistic, defined as the proportion of total variability in the results explained by heterogeneity, and not chance (45). The 95% uncertainty intervals (similar to CIs) around the I^2 were calculated using the non-central $\chi 2$ approximation of Q (46). Ninety-five per cent predictive intervals (95% PrI) were calculated for meta-analyses of three trials or more, as they incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting, which makes them crucial for the interpretation of random-effects meta-analyses (47). All analyses were performed using Stata SE 10.0 (StataCorp, College Station, TX). Statistical significance was set at a two-sided α of 5%, except for test of heterogeneity, where α was set at 10%, due to low power (48).

The overall quality of evidence (confidence in effect estimates) for the primary outcome was rated using the GRADE approach (28). The GRADE assessment was based on evidence solely from controlled clinical bias,

and not from uncontrolled cohort studies, as the latter are more prone to bias. The minimal clinical important, large, and very large effects were conventionally defined (49).

Risk of bias across studies and additional analyses

In meta-analyses of at least five studies, possible sources of heterogeneity were planned a priori to be sought through pre-specified mixed-effects subgroup analyses and random-effects meta-regression with the Knapp and Hartung (50) adjustment according to appliance and patient characteristics. If at least 10 studies were included in a meta-analysis, reporting biases (including the possibility of publication bias) were assessed using contour-enhanced funnel plots (51) and Egger's linear regression test (52). Sensitivity analyses were planned to be conducted for meta-analyses of at least 10 studies to assess their robustness according to the study design, the improvement of the GRADE classification, and signs of reporting bias.

Results

Study Selection

The initial literature search strategy yielded a total of 494 results, while five additional studies were identified from the manual search update (Supplementary Table 6). After duplicate removal and initial screening, another 44 studies were excluded after careful application of the eligibility criteria to their full-texts, leaving a total 22 papers (15-17, 53-71) (20 unique studies) included in the qualitative synthesis (Figure 1). In two instances, two studies pertaining to the same trial were grouped together (55 and 69; 57 and 71). A complete list of included and excluded studies with reasons can be found in Supplementary Table 7. From these, a total of 17 papers (15 unique studies) were included in the quantitative synthesis, as five studies did not adequately report outcome data.

Study Characteristics

The characteristics of the 20 studies included in this systematic review are given in Supplementary table 8-10. As far as study design is concerned, one was a randomized controlled clinical trial (53), two were prospective controlled clinical trials (17, 62), and the remaining 17 were cohort studies (2 retrospective (56, 60) and 15 prospective (15, 16, 54, 55, 57-59, 61, 63-68, 70) in nature). Data was collected for a total of 483 treated subjects and 55 controls (median of 20 treated and 20 control patients per study). Samples were mixed for size, gender and age of participants (Supplementary table 8). Mean initial age of treated patients ranged from 7.5-14.5 years with

an average of 11.9 years. Inclusion criteria varied, however all involved patients had transverse maxillary deficiency. In addition, posterior cross-bites were compulsory in ten studies (15, 16, 55, 57, 59-62, 66) and optional in two studies (54, 58). The level of skeletal maturation of patients prior to expansion treatment was determined by using cervical maturation index in three studies (58, 63, 64) or hand-wrist radiographs in one study (64). Separation of the maxillary halves by RME was verified, either by radiographic film (15) or recorded as clinical observation of midline diastema formation (64).

The expansion appliance used in the studies included banded RME in 9 studies (53-56, 58-60, 64, 65), bonded RME in 10 studies (15, 16, 57, 58, 61-66), while a study compared banded, bonded and Haas-style RME appliance groups (64). The cast cup design was used in a study (67) and two studies did not clearly describe type of appliance used (68, 70). Duration of active expansion varied between studies, representing varied needs of the individual patients. Reported total expansion distances at the screw ranged from 2.7-10.0 mm. While the expansion protocol was well defined in most studies, it was not reported in three of them (57, 58, 65). Retention techniques varied, with keeping the expander in place passively for some period being the most commonly used practice in 12 studies (15, 17, 53-55, 60, 62-64, 66, 68, 70), four studies did to outline a retention scheme at all (59, 61, 65, 67), while the rest of the studied provided inadequate information (16, 56-58).

The volume of seven upper airway regions was evaluated in the included studies: nasal cavity, anterior nasal cavity, maxillary sinus, nasopharyngeal, oropharyngeal, hypopharyngeal, and palatal volume. Within the nasal cavity, measurements by both AR and CT were considered. Nasal volume measures by AR were considered with decongestant or without decongestant (also known as basal condition).

All studies recorded baseline volume measurements immediately prior to commencement of RME (T1), five studies (59, 65, 67, 68, 70) assessed these volumes again immediately after active expansion (T2) and fifteen did so after the retention period (T3). The modalities used to quantify airway volume included AR in 6 studies (15-17, 53, 62, 64), CBCT in 8 studies (54, 55, 57-59, 67, 68, 70), CT in 6 studies (16, 56, 60, 61, 63, 65), surface laser scanning in one study (60), and photogrammetry in one study (66).

Risk of Bias within Studies

The risk of bias assessment for all included randomized and non-randomized trials is given in Tables 1 and 2, respectively. The inter-examiner consensus was that the risk of bias was high for all included studies. Most common biases observed were selection bias, sampling bias (due to differing inclusion / exclusion criteria),

inexistent or problematic randomization, and allocation concealment. Blinding of treatment providers and patients was not feasible, as RME use was obvious, while only one randomized trial (58) attempted during outcome assessment. Performance bias due to differences in care between groups was not deemed to be substantial within individual studies.

Results of individual studies, synthesis of results, and risk of bias across studies

The results of all included studies and the various upper airways volumes that were measured are listed in Supplementary Tables 9 and 10, respectively.

Total airway volume

The results of data synthesis regarding the primary outcome of total airway volume can be seen in Table 3. As however, no controlled clinical trials were available results are based solely on cohort studies of only treated patients and therefore should be interpreted with caution as a quantitative overview of the RME-induced changes on the upper airway. As far as total airway volume is concerned patients treated with RME showed a significant increase both post-expansion (5 studies; increase from baseline: 1218.3 mm^3; 95% CI: 702.0 to 1734.6 mm^3), which did not seem to considerably diminish after the retention period (11 studies; increase from baseline: 1143.9 mm^3; 95% CI: 696.9 to 1590.9 mm^3) (Figure 2).

Airway volumes of the various regions

As far as changes in the various upper airway regions are concerned, the results of data synthesis are given in Tables 4-5 and Supplementary table 12.

The effect of RME on the nasal airway volume could be assessed both from controlled clinical studies and cohort studies of treated patients. As far as controlled studies using AR are concerned, RME was associated with a statistically significant increase in the nasal volume compared to untreated patients both after expansion and after the retention period (Table 4). Additionally, this increase was consistent in both basal and decongested conditions of the nasal cavity. Assessment of the results with the GRADE approach indicated that the quality of evidence for this increase was “very low”, due to the nature of the included studies and serious methodological limitations (Table 5).

Additionally, based on cohort studies of treated patients RME was associated with increased nasal cavity volume measured by CT, AR in the basal condition, and AR in the decongested condition, although this was statistically significantly only for the latter. Additionally, this increase seemed to diminish slightly from post-expansion (increase of 69.0 mm^3) to post-retention (25.8 mm^3), although remaining statistically significant.

Furthermore, RME was associated with an increase in the CT-measured volume of the velopharynx (1201.2 mm^3 post-retention), the nasopharynx (662.3 mm^3 post-expansion; 396.7 mm^3 post-retention), the oropharynx (390.4 mm^3 post-expansion; 70.7 mm^3 post-retention), and the hypopharynx (170.0 mm^3 post-retention). However, most of these volumes were not statistically significantly increased from baseline, presumably due to the limited number of contributing studies, their small samples, and the resulting low statistical power. In any case, caution is warranted in the interpretation of these findings, as no control groups were included to factor out the normal growth of the upper airways.

Additional Analyses

Due to the limited number of studies in the meta-analyses, subgroup analyses could be performed only for two outcomes: the total airway volume and the total nasal cavity volume, both measured post-retention with CT (Supplementary Table 13). No significant effect on the RME-induced volume increase could be found for patient age, patient sex, and appliance design.

As far as the assessment of reporting biases (including the possibility of publication bias is concerned) only one meta-analysis with at least ten studies was included, assessing the total airway volume post-retention with CT. As can be seen in the contour-enhanced funnel plot (Figure 3) and the results of Egger's test, no considerable indications of reporting biases could be found (Supplementary table 13).

Finally, although various sensitivity analyses were initially planned, these could not be robustly performed, due to the small number and the characteristics of the included studies. The only sensitivity analysis that could be performed was the assessment of difference in the effects between prospective and retrospective studies. Prospective studies tended to report considerably smaller total volume increases after RME compared to retrospective studies (difference=-560.9 mm^3; 95% CI=-2139.5 to 1017.8 mm^3), although this was not statistically significant (P=0.442).

Discussion

Summary of Evidence

This systematic review summarized evidence on the effect of RME on the upper airway volume from clinical studies in humans. However, the results have to be considered with caution, due to the limited number of existing studies and serious methodological issues in their conduct.

In a previous systematic review, Baratieri *et al*. (27) investigated the long term effects of RME on airway dimensions and functions. The authors included studies reporting 2D linear measurements from xrays, nasal volume and minimal cross sectional areas from CBCTs and AR and functional parameters such as nasal airway resistance and airflow as measured with rhinomanometry. They concluded that moderate evidence exists as to improvement of nasal breathing after RME in growing patients and these results are stable for at least 11 months after treatment. However, in the present systematic review we expanded the selection criteria in studies that not only evaluated volumetric changes in the nasal cavity but also in all upper airway areas. Moreover, studies reporting results after a retention period of more than 8months were excluded from our study in an attempt to reduce the effect of growth and evaluate the net result of RME.

The main finding of the present review was that RME is associated with an increase in the total volume of the upper airway as well as the volume of the various regions of the upper airway. This increase seemed to be consistent to the various measurement modalities used in the studies and slightly diminished during the retention period. Although the type of expander appliance used varied amongst studies, no considerable differences were found based on appliance design. Additionally, some inconsistency existed across studies with regards to the definition of airway region borders. International consensus on region limits does not currently exist, particularly the landmarks or planes used to demarcate the junction of the nasal cavity and nasopharynx and between regions of the pharynx. This can lead to discrepancies between studies referring to similar airway spaces, although this has a smaller effect on the primary outcome of this review, which was the total airway volume. Also, various study designs were included, which have been shown to be associated with different extents of bias (41, 42), and this might explain part of the observed variability in the results.

When considering the nasal cavity volume, very low quality evidence according to the GRADE approach indicates that RME is associated with a modest but consistent increase in volume measured by AR (Table 5). This is seen in both basal and decongested conditions, while uncontrolled CT-based evidence from cohort studies seems to back up this notion (Supplementary table 12). Amongst AR studies, there seemed to be a possible correlation between the initial subject age and the magnitude of the effect size, with younger initial age producing larger effect sizes. This descriptive trend was demonstrated in both decongested and non-decongested groups. Explanation is likely due to the reduced resistance in the bony sutures. Thus, nasal cavity volume increase might

be more pronounced in growing young subjects. Additionally, RME appears to increase the volume of the anterior nasal cavity based on CT measurements. The implications of dimensional increases in this zone are important, as it represents the region of greatest nasal airflow-resistance in most people (72) and a number of authors attribute improvements in nasal breathing to nasal valve enlargement (11).

There is much debate over the validity of CT and CBCT volumetric analysis in the measurement of function airway spaces. Topical contrast agents have been suggested to improve accuracy in defining soft tissue surfaces (73), an alternative that was not used in any of the included studies. Only a few studies that use CBCT for airway volume calculation describe using any form of standardization of patient positioning and protocol during image capture. This is particularly relevant in the retrospective studies where airway standardization at capture would be unlikely to have occurred, unless future airway assessments were foreseen at the time. Vertical position in conjunction with a neck-brace and apparatus to orient natural head posture among other standards of breathing, swallowing and occlusion has been incorporated in order to obtain data with minimized variation (54). It has been shown that airway dimensions change according to head posture (74) and these changes were attributed to gravity acting on the relaxed soft palate, tongue and hyoid bone positions. More precisely, anteroposterior dimensions at the level of the velopharynx and sagittal cross-sectional areas of both velopharynx and oropharynx were decreased in response to body position change from upright to supine when measured in lateral cephalograms (75), indicating another factor that might increase heterogeneity amongst studies .

Additionally, pharyngeal airway space (PAS) dimensions are closely related to both sagittal and vertical skeletal pattern. When CBCT reconstructions were used to evaluate linearly and volumetrically the dimensions of PAS in children with different growth patterns, it was found that as the SNB angle was decreasing, linear measurements of PAS at the level of the uvula, uvula tip, mandibular line and back of the tongue also decreased. This trend was also consistent in regards to airway volume, airway area and minimum axial area. Further investigation on the effect of vertical facial type on PAS revealed that the hyperdivergent growth pattern was associated with reduced linear values at the level of the uvula tip. Conclusively, dimensions were significantly reduced in hyperdivergent patients with retrognathic mandibles (76). In the present systematic review, included studies did not provide information on grouping patients according to initial anteroposterior or vertical relationships. As airway dimensions differ according to the skeletal pattern, an additional confounding factor at the baseline of the included studies increases heterogeneity of the sample and possibly creates individual variations in patients' airway response to RME.

The ethical questions raised regarding the use of a control group relate to withholding RME treatment from a group of patients who are at an appropriate age for it for the purpose of acting as a control and to radiation exposure. Depending on the settings, full CBCT images of the head can produce dosages from 68-368 μSv (77). Keeping in mind the stochastic nature of the effect of ioniziong radiation (78, 79), it might not be appropriate to subject a control group to multiple radiation exposures in relatively close succession.

Although cross-sectional area and respiratory indices were not considered in this review, the implication of increases in volume in the airway is the potential for improvements in compromised functional respiratory features. Further research in this area is required in order to provide better evidence on the normal growth changes in volumetric parameters during the growth period and possible respiratory effects that may occur from them. Given technological advancements in diagnostics and accuracy, it is hoped that careful attention to experimental design and conduct will allow for future results of sufficient strength to answer these questions more definitively.

As far as the generalizability/applicability of results is concerned, the results of this review might be applicable to the average growing patient with transverse maxillary constriction, as the eligibility criteria used for study selection were broad and most included studies were conducted in pragmatic conditions. As a random-effects model was used for the meta-analysis, the 95% prediction intervals should be used for interpretation; these incorporate existing heterogeneity and provide the range of possible effects of RME on airway volume. However, caution should be exerted during the interpretation of the results, due to the high risk of bias and the fact that subgroup analyses could not be adequately used to describe the ideal candidates for RME.

Strengths and Limitations

The strengths of this systematic review include the extensive literature search, the duplicate and blinded review procedures, and the assessment of the quality of evidence with the GRADE approach. All procedures of the qualitative synthesis were conducted under the guidelines of the Cochrane Handbook (29) and the PRISMA statement (30), while attempts were made to minimize bias during quantitative synthesis (80), and no signs of reporting bias were identified.

The main shortcoming of this systematic review is the limited number of existing studies, most of which are non-randomized studies with serious methodological limitations. Additionally, most existing studies do not have a control group to reduce the confounding effect of normal growth. As the aim of this review was to determine the immediate effect of RME on airway volume, it was assumed that within the short experimental

period of up to 8 months of the included studies the degree of growth effects occurring would be small. The dimensions of children's airways between 6 and 15 years increase at a normal rate of 0.032 cm^2/year (81) indicating that the volume increase found in the present study cannot be attributed to growth alone. However, this cannot be completely ruled out and future well-designed prospective controlled studies are needed to confirm this finding. Additionally, it was not possible to correlate overall the volumetric changes observed with the amount of RME activation because complete data on amount and appliance type was not provided by all studies. Finally, while sources of heterogeneity and robustness of the results were planned to be checked with subgroup and sensitivity analyses, respectively, most of these analyses could not be performed. The clinical heterogeneity at the level of assessed appliances, expansion protocols, chosen outcomes, and measurement methods is evident and precludes any robust clinical suggestions on the effect of RME on upper airway volume.

Conclusions

Evidence from existing controlled and uncontrolled clinical studies indicates that RME in growing patients with transversal maxillary constriction might be associated with a short-term increase in the total upper airway volume and most of the separate airway volumes. However, the results should be interpreted with caution, due to the small number of included trials and serious methodological issues, which might affect the risk of bias. Future well-conducted prospective controlled clinical studies on growing patients are needed in order to recommend the use of RME to increase the upper airway volume in an evidence-based and predictable way.

Supplementary material

Supplementary material is available at European Journal of Orthodontics online.

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Conflict of interest

The authors confirm that there is no conflict of interest.

Figure Legends

Figure 1. Flowdiagram for the identification and selection of studies.

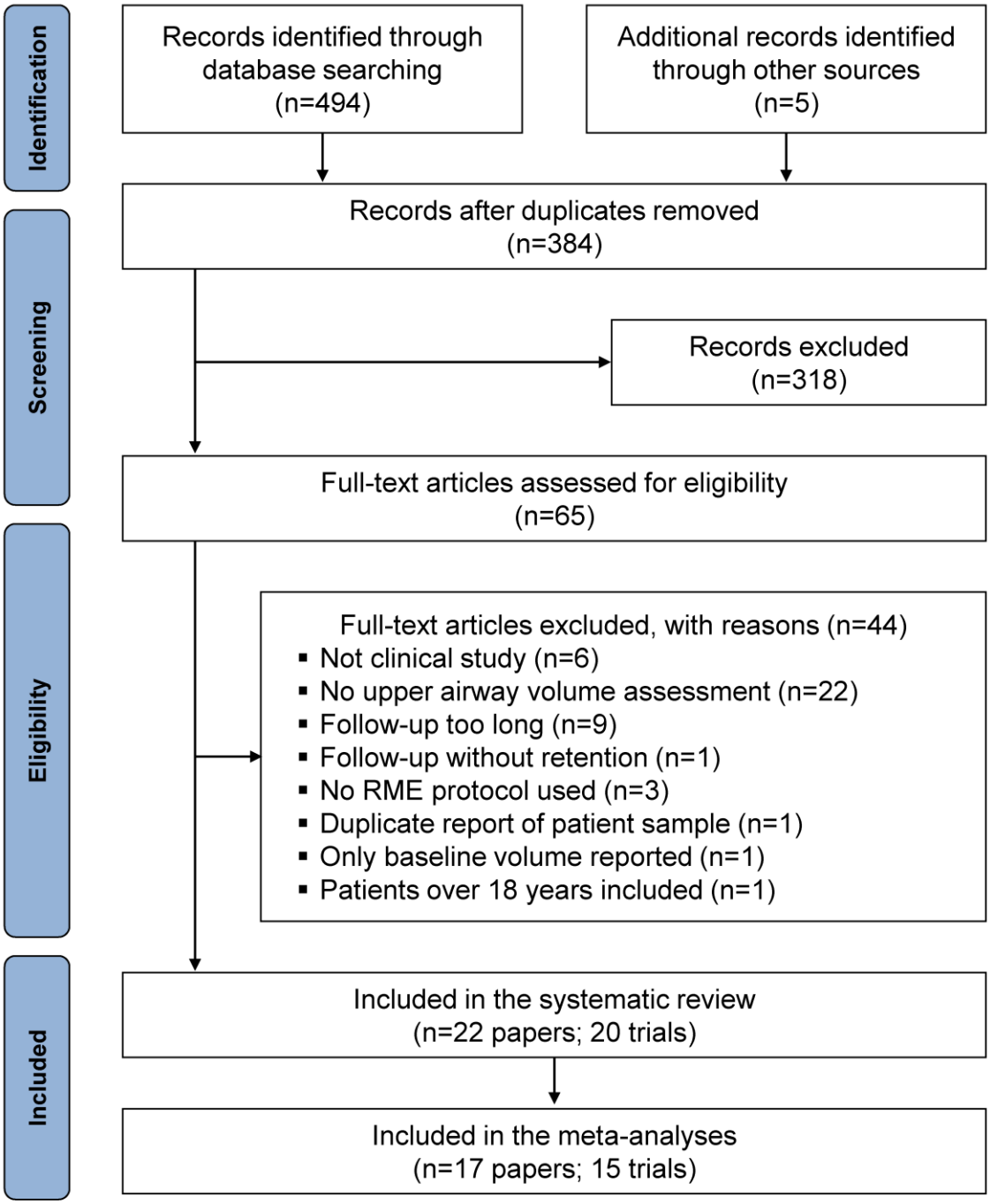

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Figure 2. Contour-enhanced forest plot for the meta-analysis of the primary outcome (post-pre total airway volume change in mm^3) in the patients treated with rapid maxillary expansion. Contours indicate increasing effect magnitude from the middle line-of-no-effect outwards (±2000.0 mm^3, ±4000.0 mm^3, ±8000.0 mm^3 used as cut-offs to indicate moderate, large, and very large effects). Studies to the right indicate that the upper airway volume was increased compared to baseline. RME, rapid maxillary expansion; CI, confidence interval; NR, not reported.

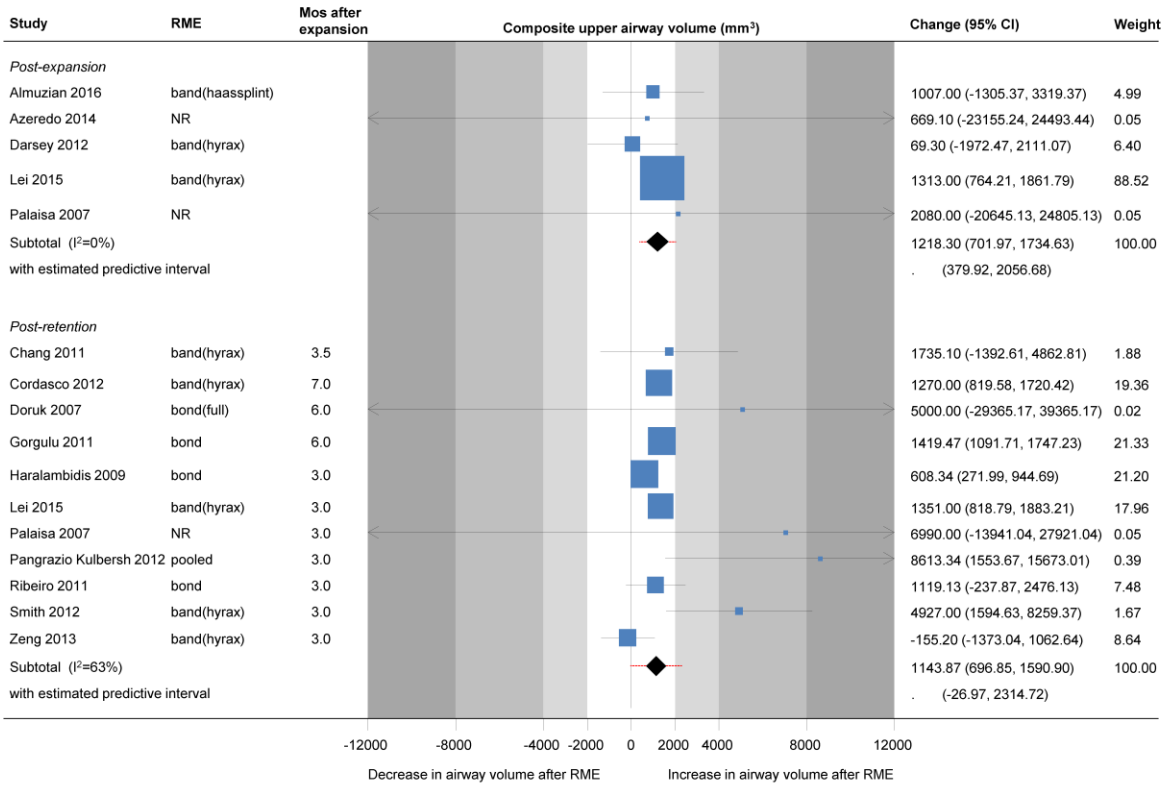

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Figure 3. Contour-enhanced funnel plots for the assessment of reporting biases (including small-study effects and the possibility of publication bias).

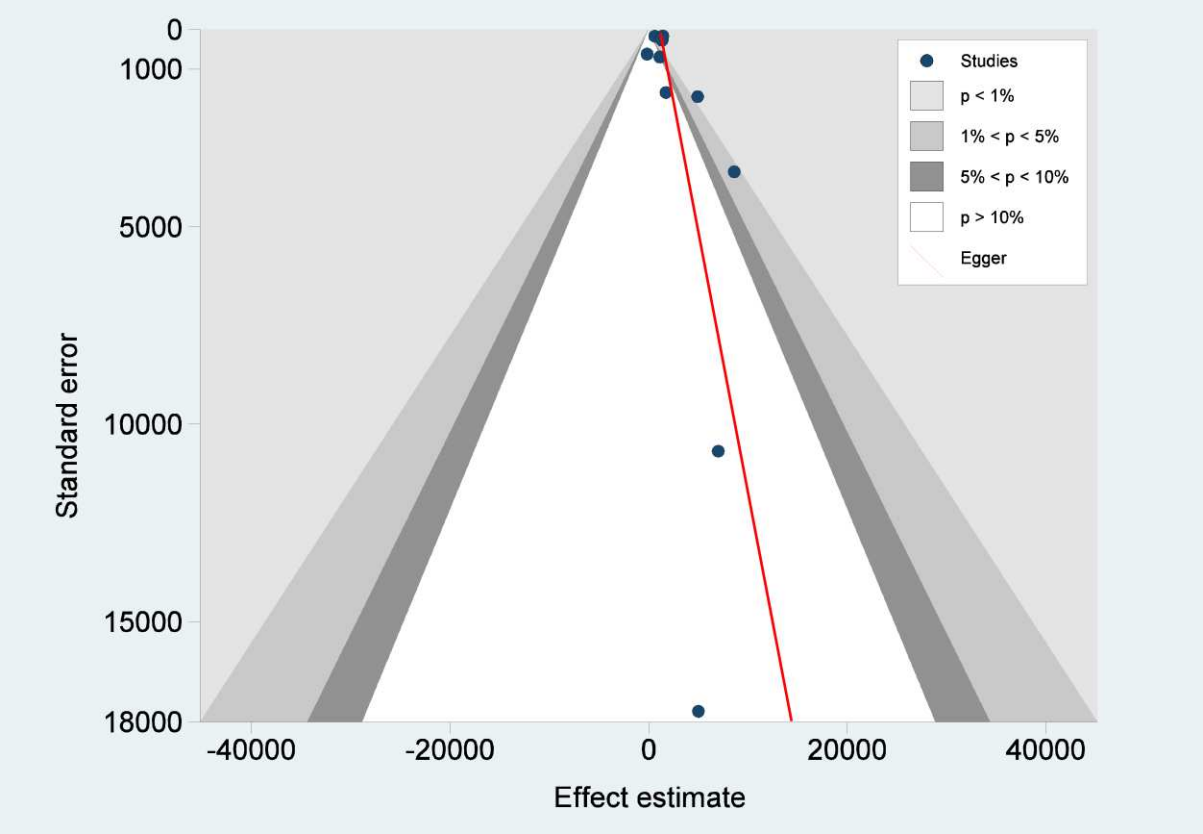

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Table 1. Risk of bias of the included randomized clinical trial.

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Blinding of outcome assessment	Other bias
Kabalan et al 2015 (52)	Low risk	High risk	High risk	Low risk	Low risk	High risk	Moderate risk

Table 2. Risk of bias assessment of the included non-randomized studies.

Study	Randomization	Sample Described	Selection Criteria	Sample Size	Controls Used	Follow-up Definition & Length	Dropouts Mentioned	Intervention Protocol Described	Measurement Defined	Assessor Blinding	Reliability/Error Testing	Appropriate Statistics	Confounders Analysed	Presentation of Data	Reasonable Conclusion	Total	Methodological adequacy
Almuzian *et al* 2016 (66)	0	2	2	1	0	2	1	2	2	0	1	1	2	2	1	18	*Moderate*
Azaredo 2014 (67)	0	2	1	2	0	2	1	1	2	0	1	1	0	1	1	16	*Moderate*
Babacan *et al.* 2006 (15)	0	2	1	1	1	2	0	2	2	0	1	1	1	1	1	16	*Moderate*
Cappellette *et al.* 2008 (17)	0	2	1	2	2	2	0	1	2	0	0	1	1	1	1	16	*Moderate*
Chang 2011 (68); Chang *et al.* 2013 (54)	0	2	1	1	0	2	1	2	2	0	1	1	2	2	1	18	*Moderate*
Cordasco *et al.* 2012 (59)	0	2	1	1	0	1	1	2	2	0	1	1	1	1	1	15	*Moderate*
Darsey *et al.* 2012 (58)	0	2	1	2	0	1	0	2	2	0	1	1	1	1	1	15	*Moderate*
Doruk *et al.* 2007 (16)	0	2	1	1	0	2	0	1	1	0	1	1	1	2	1	14	*Moderate*
Görgülü *et al.* 2011 (60)	0	2	1	1	0	1	0	1	2	0	1	1	0	1	1	12	*Low*
Haralambidis *et al.* 2009 (62)	0	2	1	1	1	2	0	2	2	0	1	1	1	1	1	16	*Moderate*
Kabalan *et al* 2015 (52)	1	1	2	1	2	2	1	1	2	0	1	1	1	1	1	18	*Moderate*
Li *et al* 2015 (69)	0	2	2	2	0	2	1	2	2	0	0	1	0	1	1	16	*Moderate*
Marini *et al.* 2007 (65)	0	2	1	2	0	2	0	1	1	0	0	1	2	1	1	14	*Moderate*
Oliveira De Felippe *et al.* 2008 (63)	0	2	1	2	1	2	1	2	2	0	1	1	1	1	1	18	*Moderate*
Palaisa *et al.* 2007 (64)	0	1	1	1	0	1	1	0	2	0	1	1	0	2	1	12	*Low*
Pangrazio-Kulbersh *et al.* 2012 (57)	1	2	1	1	1	2	0	1	2	1	1	1	1	1	1	17	*Moderate*
Ribeiro 2011 (70); Ribeiro *et al.* 2012 (56)	0	1	1	1	1	1	0	1	1	0	0	1	1	1	1	11	*Low*
Smith *et al.* 2012 (55)	0	2	1	1	0	2	1	2	2	0	1	1	2	1	1	17	*Moderate*
Sökücü *et al.* 2010 (61)	0	2	1	1	2	2	0	2	2	0	1	1	2	1	1	18	*Moderate*
Zeng & Gao 2013 (54)	0	2	1	1	0	2	0	2	2	0	0	1	2	1	1	15	*Moderate*
MAXIMUM	**1**	**2**	**2**	**2**	**2**	**2**	**1**	**2**	**2**	**1**	**1**	**1**	**2**	**2**	**1**	**25**	

Table 3. Results of meta-analyses regarding the main outcome (total airway volume in mm^3) only in treated groups.

Measurement	Timing	Studies	Change (95% CI)	P	95% Predictive Interval	I^2 (95% interval)
CT	Post-expansion	5	1218.30 (701.97,1734.63)	<0.001	379.92,2056.68	0% (0%,64%)
CT	Post-retention	11	1143.87 (696.85,1590.90)	<0.001	-26.97,2314.72	63% (14%,79%)

CI, confidence interval; CT, computed tomography; AR, acoustic rhinometry.

Table 4. Results of meta-analyses on total nasal cavity volume in mm^3 from studies with untreated controls (change in treated patients minus change in untreated patients)*.

Measurement	Timing	Studies	MD (95% CI)	P value
AR-basal condition	post-expansion	1	44.00 (32.65,55.35)	<0.001
AR-basal condition	post-retention	1	19.00 (7.80,30.20)	0.001
AR-decongested condition	post-expansion	1	71.00 (57.28,84.72)	<0.001
AR-decongested condition	post-retention	1	23.00 (9.45,36.55)	0.001

MD, mean difference; CI, confidence interval; AR, acoustic rhinometry.

* I^2 with its associated 95% intervals and 95% predictive intervals could not be calculated.

Table 5. Summary of Findings table according to the GRADE approach for the primary outcome results from studies with untreated control group.

Patients: patients with posterior crossbite or an anteriorly constricted maxillary arch in need of maxillary expansion

Settings: university clinic (Turkey)

Intervention: conventional of fan-type rapid maxillary expansion

Comparison: patients with ideal occlusion that did not receive any treatment

Outcomes, no of participants (studies)	Relative effects (95% CI)	Anticipated absolute effects		Quality of evidence (GRADE)	What happens
		Observation	RME		
Nasal cavity volume measured by AR (basal) Follow-up: post-expansion; 23.3 days 45 patients (1 study)	MD 44.0 (32.7 to 55.4)	5.0 mm^3 increase	49.0 mm^3 increase (37.7 to 60.4 mm^3 increase)	⨁⊖⊖⊖ very low[a]	Probably increases nasal cavity volume
Nasal cavity volume measured by AR (basal) Follow-up: post-retention; 6.2 months 45 patients (1 study)	MD 19.0 (7.8 to 30.2)	6.0 mm^3 increase	25.0 mm^3 increase (13.8 to 36.2 mm^3 increase)	⨁⊖⊖⊖ very low[a]	Same
Nasal cavity volume measured by AR (decongested) Follow-up: post-expansion; 23.3 days 45 patients (1 study)	MD 71.00 (57.3 to 84.7)	2.0 mm^3 decrease	2.0 mm^3 decrease	⨁⊖⊖⊖ very low[a]	Same
Nasal cavity volume measured by AR (decongested) Follow-up: post-retention; 6.2 months 45 patients (1 study)	MD 23.00 (9.5 to 36.6)	2.0 mm^3 increase	2.0 mm^3 increase	⨁⊖⊖⊖ very low[a]	Same

CI, confidence interval; AR, acoustic rhinometry; MD, mean difference; RME, rapid maxillary expansion.
GRADE starts from "low", due to the inclusion of non-randomized studies. Downgraded further by one point for high risk of bias.

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Supplementary Table 1. Medline search strategy via Ovid

Step	Keyword (hits)
1	RME.mp (637)
2	rapid maxillary expan$.mp (554)
3	rapid palatal expan$.mp (284)
4	maxillary expan$.mp (814)
5	skeletal expan$.mp (36)
6	palatal expan$.mp (2087)
7	transverse expan$.mp (71)
8	orthodontic expan$.mp (50)
9	orthop?edic maxillary expan$.mp (6)
10	transpalatal distract$.mp (20)
11	rapid maxillary disjunction.mp (0)
12	rapid palatal disjunction.mp (1)
13	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 (2651)
14	air$.mp (352190)
15	volum$.mp (479228)
16	14 OR 15 (795866)
17	13 AND 16 (216)
18	Limit 17 to English language (199)

Supplementary Table 2. Embase search strategy.

Step	Keyword (hits)
1	Maxillary (45918)
2	Palatal (10714)
3	Rapid (574980)
4	Expan* (320271)
5	Skeletal (219238)
6	Orthodontic (35390)
7	Orthop?edic (166763)
8	Transverse (59857)
9	Transpalatal (488)
10	Distract* (25324)
11	Disjunction (2069)
12	#1 AND #3 AND #4 (842)
13	#2 AND #3 AND #4 (467)
14	#1 AND #4 (2099)
15	#1 OR #2 (53992)
16	#4 AND #5 AND #15 (443)
17	#2 AND #4 (824)
18	#4 AND #8 AND #15 (398)
19	#4 AND #6 (1374)
20	#1 AND #4 AND #7 (27)
21	#9 AND #11 (1)
22	#1 AND #3 AND #11 (18)
23	#2 AND #3 AND #11 (11)
24	#12 OR #13 OR #14 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 (2862)
25	air* (634013)
26	volum* (837843)
27	#25 OR #26 (1411050)
28	#24 AND #27 (331)
29	#24 AND #27 AND [humans]/lim AND [English]/lim (257)

Supplementary Table 3. Eligibility criteria used for the study selection

Category	Inclusion criteria	Exclusion criteria
Participant characteristics	Studies with at least 8 human growing patients (age ‹ 18years) with constricted maxilla (unilateral or bilateral posterior crossbite) in need for orthopaedic expansion	Clinical trials with less than 8 patients Patients with craniofacial syndromes and/or cleft lip and palate Medically compromised patients Patients with temporomandibular joint disorders Animal studies
Intervention	Jackscew-based Rapid Maxillary Expansion (RME) RME appliance left in place for retention (maximum 8 months post-RME)	Other concurrent orthodontic treatments received that may influence results (eg. orthodontic fixed appliances) Slow maxillary expansion Expansion with removable appliances
Comparison	• Same patients compared at baseline and after RME (immediately or maximum 8 months post-RME) • Patients treated with surgically assisted rapid maxillary expansion • Untreated controls	Follow-up measurements taken more than 8 months after expansion Follow up measurements not taken either immediately after active expansion or immediately after retention period, thus involving significant period without transverse retention
Outcome	Studies providing quantitative volumetric measurements of the upper airways from: • Acoustic rhinometry • Computed tomography • Cone beam computed tomography • Digital photogrammetric technique	Studies providing only linear cephalometric measurements Studies providing only study model linear measurements
Study design	Randomized controlled clinical trials Prospective or retrospective controlled clinical trials Clinical cohort studies	Case reports Review articles Unsupported opinions Interviews Commentaries Conference abstracts Replies to the editor/author

Supplementary Table 4. Data extraction form.

Item
Study Name:
Author & Year:
Date form completed:
Sample Group (age, gender, ethnicity, etc):
Control/Comparator Group (age, gender, ethnicity, etc):
Methods of recruitment of participants:
Inclusion Criteria:
Exclusion Criteria:
Informed consent obtained? (Yes/No/Unclear)
Ethical approval (Yes/No/Unclear)
Funding (if stated)
Statistical methods and their appropriateness (if relevant):
Principal health problem or diagnosis (if relevant):
Other health problem/s (if relevant):
Purpose of study (if stated):
Treatment received/receiving:
Volume Measurement Technique(s) used:
Region that Volume Measured:
Definition/Boundaries of Measured Region(s):
Other Measurements Taken:
RME Technique Used:
Expansion Appliance Details:
Activation Protocol:
Activation End-point:
Retention Protocol (method & timing):
T2 Measurement Time-Point:
T3 Measurement Time-Point:
AR Specifics (measurement technique):
CT Specifics (measurement & calculation technique):
3D Photographic/ Scanning Specifics (measurement & calculation technique):
Error Assessment:
Comments:

AR, acoustic rhinometry; CT, computed tomography; 3D, three-dimensional.

Supplementary Table 5. Risk of Bias Assessment Tool.

1. Study Design
    a. Randomization to groups (0/1)
        0 = No randomization or inadequate randomization
        1 = Adequate randomization to groups
    b. Sample Described (0/1/2)
        0 = No details provided of study sample
        1 = Some descriptive statistics of study sample given but incomplete
        2 = Sample adequately described & statistics provided (age, gender etc)
    c. Selection Criteria (0/1/2)
        0 = No details on how study participants were recruited
        1 = Some information provided on subject inclusion & exclusion but no bias reduction methods used or described
        2 = Inclusion & exclusion criteria disclosed & bias reduction methods implemented (ie. Consecutive selection of patients)
    d. Sample Size (0/1/2)
        0 = Sample size <8
        1 = Sample size 8-25
        2 = Sample size >25 patients
    e. Controls Used (0/1/2)
        0 = No control
        1 = Attempt made to use some form of control/comparator group
        2 = A matched, untreated control group used
    f. Follow-up Definition & Length (0/1/2)
        0 = No follow-up period or study end-point given
        1 = Follow-up period poorly defined or inadequate
        2 = Clear description of initiation of Tx and follow-up time & how statistics were computed
2. Study Conduct
    a. Dropouts Mentioned (0/1)
        0 = No description of subject drop-outs or lost to follow-up, or excessive >20% drop-out during follow-up
        1 = No dropouts or acknowledgement of dropouts
    b. Intervention Protocol Described (0/1/2)
        0 = No details given on appliance or its use
        1 = Details given on expansion appliance and activation protocol clearly described
        2 = Details on expansion appliance and activation protocol clearly described, along with amount of activation or end-point for activation
    c. Measurement Defined (0/1/2)
        0 = No description of how volumes or changes were quantified
        1 = Partial measurement details given
        2 = Clear description of volume measurement technique including apparatus used & technique
    d. Assessor Blinding (0/1)
        0 = No blinding used in assessing to outcomes
        1 = Attempt to blind outcome assessors
    e. Reliability/Error Testing (0/1)
        0 = No error testing or method error provided
        1 = Reporting & statistical examination of errors
3. Statistical Analysis
    a. Appropriate Statistics (0/1)
        0 = Statistical methods not disclosed or inappropriate methods used
        1 = Correct & judicious use of statistical tests & avoidance of type I errors
    b. Confounders Analyzed (0/1/2)
        0 = Not discussed
        1 = Confounders discussed but no statistical adjustments made in analysis
        2 = Acknowledgement of, and statistical adjustment made for confounding variables
    c. Presentation of Data (0/1/2)
        0 = Poor presentation of data with key variables omitted
        1 = Majority of data displayed, only 'grouped' values given rather than individual subject results
        2 = Clear presentation of data, point estimates, variances, change scores & individual subject data provided
4. Conclusion
    a. Reasonable Conclusion for Study Power (0/1)
        0 = No conclusion made, or unreasonable conclusions given study design
        1 = Reasonable statement of study meaning in light of limitations

Tx, treatment.

Supplementary Table 6. Results of the literature searches performed in each database.

Database	Date searched	Results
MEDLINE (through Ovid)	February 1st, 2015	199
Embase	February 1st, 2015	257
PreMEDLINE	February 1st, 2015	25
CENTRAL	February 1st, 2015	13
OLDMEDLINE	February 1st, 2015	0
Manual search in Google Scholar for additions	February 1st, 2016	5

Supplementary Table 7. Studies Excluded with Reasons (total: 44 studies).

Study	Database(s) Found	Rating after full-text review	Reason
Al-Taai et al. 2015	PML	NO	2
Altug-Atac, et al. 2010	Hand	NO	2
Atac et al 2011	E	NO	2
Bicakci et al. 2005	ML, CEN, E	NO	2
Bouserhal et al. 2014	ML, E	NO	2
Caprioglio et al. 2014	ML, E	NO	3
Chiari et al. 2009	ML, E	NO	2
Compadretti et al. 2006	ML, E	NO	3,4,5
Compadretti,Tasca, et al. 2006	ML, E	NO	3,4,5
Cozza et al. 2007	E	NO	2
De Felippe et al. 2009	ML, E	NO	3,7
Doruk et al. 2004	ML, E	NO	2
El & Palomo 2014	ML	NO	3,4,5
Enoki et al. 2006	ML, E	NO	2
Fastuca et al. 2014	PML	NO	7
Ghoneima et al. 2010	ML, E	NO	2
Giuca et al. 2009	ML, E	NO	2
Gohl et al. 2010	ML, E	NO	3,4,5
Gracco et al. 2010	ML, E	NO	3
Gray & Brogan 1972	ML	NO	2
Gray 1975	E	NO	2
Iwasaki et al. 2013	ML, E	NO	3,4,5
Iwasaki et al. 2012	ML, E	NO	2
Iwasaki et al. 2014	ML, E, PML	NO	2
Kurt et al. 2010	ML	NO	2
Matsumoto et al. 2010	ML, E	NO	2
Motro et al. 2015	E	NO	10,11
Neveus et al. 2014	E	NO	8
Petit, 1987	ML	NO	1
Pirelli et al. 2010	ML, E	NO	2
Primozic, Baccetti et al. 2013	ML	NO	4,6
Primozic, Ovsenic et al. 2009	ML, E	NO	6
Primozic, Perinetti et al. 2013	ML, E	NO	6
Primozic, Richmond et al. 2013	E	NO	6
Rondeau, 2004	ML	NO	1
Subtelny, 1980	ML	NO	1
Tecco et al. 2005	E	NO	2
Timms, 1987	ML	NO	1
Timms, 1995	ML	NO	1
Timms, 1984	ML, E	NO	2
Timms, 1986	ML	NO	1
Warren et al. 1987	ML, E	NO	2
Wertz, 1968	ML, E	NO	2
Zhao et al. 2010	ML, E	NO	3,4,5

PML, PreMEDLINE; Hand, handsearching; E, Embase; ML, MEDLINE; CEN, Central.

Key to reason for exclusion of study at full-text review
1. Not a clinical study
2. Not assessing or measuring upper airway volume(s)
3. Follow-up period too long (>8months)
4. Follow-up period involves significant period without any retention
5. Additional treatment performed besides RME during study period
6. Does not use RME protocol (ie. SME, SRME)
7. Duplicate sample or sample data used
8. Only baseline volume(s) reported
9. Could not be located in English
10. Sample included patients over 18 years
11. Appliance type not consistent with inclusion

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Supplementary Table 8. Study Design, Participants, Intervention, Comparators and Outcome (PICO) of Included Studies.

Study	Country	Study Design	Treatment Group	Control	Inclusion Criteria	Intervention	Outcome (Volume)
Almuzian *et al.* 2016 (67)	UK	Prospective cohort study	17 Pts (8 boys, mean age 12.4yrs Range:10.5-14.08yrs) (9 girls, mean age 12.8yrs Range: 10-16.25yrs)	No	Caucasians, age 10-16yrs, Normal body mass index Constricted maxillary arch Unilateral or bilateral posterior crossbite No previous surgery (tonsilar, nasal, adenoid, head and neck) No craniofacial deformity No previous orthodontic treatment Less than 5° head and craniocervical orientation between pre-treatment and post-treatment	RME (cast cup)	Lower nasal cavity Upper nasopharynx Retropalatal Right and left sinus
Azaredo 2014 (68)	Brazil	Prospective cohort study	33 Pts (11 boys, 22 girls) mean age 10.7±1.63yrs)	No	Transverse maxillary deficiency Upper first permanent molars and first premolars or first primary molars present and fully erupted Age 7-14 years old No previous orthodontic treatment No congenital malformations No tooth agenesis No periodontal problems	RME (Hyrax or Hass as assumed by ethics approvals in the appendices)	Total upper airway
Babacan *et al.* 2006 (15)	Turkey	Prospective cohort study	10 Pts (5 boys, 5 girls) mean age 12.3 ± 0.82yrs	No	No history of nasal disease No previous tonsillar, nasal or adenoidal surgery Presence of adequate nasal cavity space confirmed by anterior rhinoscopic examination by otolaryngologist Skeletal maxillary constriction with bilateral posterior crossbite	RME (bonded)	Nasal cavity
Cappellette *et al.* 2008 (17)	Brazil	Prospetive controlled clinical trial	50 Pts (27 boys, 23 girls) age range 4-14 yrs	20 Pts (11boys , 9girls) Age 4-11 yrs Without Maxillary hypoplasia	Mouth breathing pts Age 4-14yrs Clinical diagnosis of maxilla hypoplasia by an orthodontist	RME	Nasal cavity
Chang 2011 (69);	USA	Prospective cohort	14 Pts	No	Young orthodontic pts (<16yrs),	RME (banded)	Retropalatal

Chang *et al.* 2013 (55)		study	(5 boys, 9 girls) mean age 12.9ysr (range 9.7-16yrs)		Unilateral or bilateral posterior crossbites, Pts scheduled to receive RME as part of comprehensive orthodontic treatment		Retroglossal Total upper airway
Cordasco *et al.* 2012 (60)	Italy	Retrospective cohort study	8 Pts (3males, 5 girls) mean age 9.7yrs (SD 1.41yrs)	No	Constricted maxillary arch All first permanent molars erupted, Unilateral or bilateral posterior crossbite	RME (banded)	Anterior Nasal cavity Posterior Nasal cavity Total Nasal cavity
Darsey *et al.* 2012 (59)	USA	Prospective cohort study	30 Pts (10 boys, 20 girls) mean age 13.8yrs (range 9-20y) Group 1: 9-14yrs (n=18, 6 boys,12 girls) Group 2: 15-20yrs (n=12, 4 boys, 8 girls)	No	Patients with bilateral posterior crossbites Determined to require bilateral maxillary expansion by orthodontist	RME (banded)	Maxillary sinuses
Doruk *et al.* 2007 (16)	Turkey	Prospective cohort study	10 Pts (4 boys, 6 girls) age range 12-14yrs	No	Maxillary transverse narrowness with bilateral posterior crossbite No previous history of nasal disease	RME (bonded)	Nasal cavity
Görgülü *et al.* 2011 (61)	Turkey	Prospective cohort study	15 Pts (9 boys, 6 girls) mean age 13.86y +/- 1.4yrs (range 12-16y)	No	Maxillary constriction, Bilateral posterior crossbite, Requiring rapid maxillary expansion treatment, Clinical crown length able to provide sufficient anchorage for the RME appliance	RME (bonded)	Nasal cavity
Haralambidis *et al.* 2009 (63)	Turkey	Prospective cohort study	24 Pts (10 boys, 14 girls) Mean age 14.5yrs Class I =10, Class II =14 (CVM: cervical vertebrae maturation; CVM3:9 Pts, CVM4:9 Pts, CVM5:6 Pts)	No	No specified	RME (bonded)	Anterior nasal cavity
Kabalan *et al.* 2015 (53)	Canada	Randomised controlled trial	61 Pts 11-17 years	20 (random allocation from total sample)	Diagnosed need for maxillary expansion due to skeletal transverse deficiency	RME (tooth-borne) RME (bone-	Nasal Cavity

					Full permanent dentition erupted.	borne)	
Li *et al.* 2015 (70)	China	Prospective cohort study	35 Pts (18 boys,17 girls) mean age 12.1±1.1yrs	No	Narrow maxilla Unilateral or bilateral crossbite Growth potential (cervical vertebrae maturation index) Clear and complete CBCT records No cleft lip and/or palate No facial damage No issues with trauma, adenoids or other factors affecting craniofacial development	RME (Hyrax)	Nasopharynx Oropharynx
Marini *et al.* 2007 (66)	Italy	Prospective cohort study	30 Pts (14 boys, 16 girls) mean age 7.5yrs range 7-8yrs	No	Posterior crossbite, due to narrow maxilla	RME (bonded)	Palatal
Oliveira De Felippe *et al.* 2008 (64)	USA	Prospective cohort study	38 Pts (19 boys, 19 girls) mean age 13yrs (boys:8-16yrs, girls:9-15yrs)	No	Growing patients who were to receive rapid maxillary expansion treatment. No history of upper respiratory diseases or anomalies	RME (Haas) RME (banded) RME (bonded)	Nasal cavity Palatal
Palaisa *et al.* 2007 (65)	USA	Prospective cohort study	19 Pts (sexes not given) aged 8-15yrs (detailed age stats not given)	No	Require banded or bonded hyrax palatal expander as part of their comprehensive orthodontic treatment. Require at least 4mm of maxillary expansion. No previous orthodontic treatment or craniofacial growth anomalies	RME (banded or bonded)	Nasal cavity
Pangrazio-Kulbersh *et al.* 2012 (58)	USA	Prospective cohort study	Banded RME: 13 Pts (7 boys, 6 girls) mean age 12.6 +/- 1.8yrs Bonded RME: 10 Pts (5 boys, 5 girls) mean age 13.5 +/- 2.1yrs	No	Constricted maxillary arch (with or without cross-bites,) Full permanent dentition	RME (banded) RME (bonded)	Maxillary sinuses Posterior Airway
Ribeiro 2011 (71);	Brazil	Prospective cohort	15 mixed dentition Pts	No	Transverse maxillary deficiency	RME (bonded)	Nasopharynx

Ribeiro *et al.* 2012 (57)		study	(7 boys, 8 girls) mean age 7.5yrs (no range or SD given)		Unilateral posterior crossbite		Oropharynx
Smith *et al.* 2012 (56)	USA/ Egypt	Retrospective cohort study	20 Pts (8 boys, 12 girls) mean age 12.37yrs range 8-15yrs (SD 1.9months)	No	Pts with bilateral maxillary constriction, No previous orthodontic/orthopaedic treatment. No systemic diseases, craniofacial anomalies or TMJ disorders. No tonsillectomy or adenoidectomy. No carious, gingival or periodontal lesions. No metallic restorations. RME planned as part of comprehensive orthodontic treatment	RME (banded)	Nasal cavity Maxillary sinuses Nasopharynx Oropharynx Hypopharynx
Sökücü *et al.* 2010 (62)	Turkey	Prospective controlled clinical trial	15 Pts (7 boys, 8 girls) Mean age 12.41 +/- 0.98yrs	15 Pts (8 boys, 7 girls) Mean age = 12.46 +/- 0.56yrs Ideal untreated occlusions	RME group had posterior cross-bites	RME (bonded)	Nasal cavity
Zeng & Gao 2013 (54)	China	Prospective cohort study	16 Pts (10 boys, 6 girls) mean age 12.73 +/- 1.73yrs (range 10-15)	No	Constricted Maxilla (with or w/o posterior cross-bite) Upper first molars & first premolars erupted	RME (banded)	Lower Nasal cavity Nasopharyngeal Oropharyngeal

yr, year; RME, rapid maxillary expander; SD, standard deviation; Pt, patient; CVM, cervical vertebral maturation.

Supplementary Table 9. Measurement Techniques, Time-points, Airway Regions & Key Result Summary of Included Studies.

Study	Measurement Technique	Follow-up Points	Region Volume Measured	Treated Group Recorded Changes	Approx % Change*	Outcome
Almuzian *et al* 2016 (67)	CBCT	T1- Prior to RME T2- After complete expansion	Left maxillary sinus Right maxillary sinus Lower nasal cavity Upper nasopharynx Upper retropalatal Lower retropalatal	T2-T1: 6855±3728 vs 6940±4207 mm^3 T2-T1: 7133±3348 vs 6855 ±3681 mm^3 T2-T1: 5600±3374 vs 4785 ±2195 mm^3 T2-T1: 3101±1374 vs 2736 ±1395 mm^3 T2-T1: 492±731 vs 527 ±827 mm^3 T2-T1: 2994±2226 vs 3305 ±2265 mm^3	-1.2% 3.8% 17% 13.4% -6.6% -9.4%	Not-effective (*P*=0.82) Not-effective (*P*=0.5) Not-effective (*P*=0.06) Effective (*P*=0.04) Effective (*P*=0.04) Not-effective (*P*=0.27)
Azaredo 2014 (68)	CBCT	T1- Prior to RME T2- After complete expansion	Total upper airway vol	T1-T2: 7451.6±3490.7 vs 8120±3764.7 mm^3	n/a	Not-effective (*P*=0.109)
Babacan *et al.* 2006 (15)	AR (ND & D)	T1- Prior to RME T2- n/a T3- After 6m retention	Nasal cavity vol	T1-T3 (ND): 0.16 ± 0.02 vs 0.18 ± 0.02 cc T1-T3 (D): 0.18 ± 0.02 vs 0.21 ± 0.02 cc	12.5% 17%	Effective (*P*<0.05) Effective (*P* <0.05)
Cappellette *et al.* 2008 (17)	AR (D)	T1- Prior to RME T2- After complete expansion T3- n/a	Right nasal cavity vol 1 Right nasal cavity vol 2 Left nasal cavity vol 1 Left nasal cavity vol 2	T1-T2: n/a T1-T2: n/a T1-T2: n/a T1-T2: n/a	n/a n/a n/a n/a	Effective (*P*=0.002) Effective (*P*=0.023) Effective (*P*=0.004) Not-effective (*P*=0.189)
Chang 2011 (69); Chang *et al.* 2013 (55)	CBCT	T1- Prior to RME T2- n/a T3- After 3-4m retention	Retropalatal vol Retroglossal vol Total upper airway vol	T1-T3: 1201.2 ± 3018.82 mm^3 T1-T3: 533.8 ± 3486.82 mm^3 T1-T3: 1735.1 ± 5970.95mm^3	19% 10.9% 15.5%	Not-effective (*P*=0.1604) Not-effective (*P*=0.5765) Not-effective (*P*=0.2967)
Cordasco *et al.* 2012 (60)	CT	T1- Prior to RME T2- n/a T3- After 7m	Anterior Nasal cavity vol Posterior Nasal cavity vol Total Nasal cavity vol	T1-T3: 0.58 ± 0.33 cm^3 T1-T3: 0.69 ± 0.34 cm^3 T1-T3: 1.27 ± 0.65 cm^3	7% 8.8% 8%	Effective (*P*<0.05) Effective (*P* <0.05) Effective (*P* <0.05)
Darsey *et al.* 2012 (59)	CBCT	T1- Prior to RME T2- After complete expansion T3- n/a	Right Mx sinus vol Left Mx sinus vol Total Mx sinus vol	T1- T2: 12460.8 ± 3891.5 vs 12582.8 ± 3856.2 mm^3 T1- T2: 12953.4 ± 4939.8 vs 12900.7 ± 4270.2 mm^3 T1- T2: 25414.2 ± 8447.8 vs 25483.5 ± 7490.9	0.9% -0.4% 0.3%	Not-effective (*P*=0.763) Not-effective (*P*=0.923) Not-effective (*P*=0.929)
Doruk *et al.* 2007 (16)	CT AR (ND & D)	T1- Prior to RME T2- n/a T3- After 6m retention	Nasal cavity vol (CT) Nasal cavity vol (AR)	T1-T3: 38.9 ± 7.14 vs 43.9 ± 8.26 cm^3 T1-T3 (D): 38.5 ± 7.46 vs 46.5 ± 9.48 cm^3	13% 21%	Effective (*P*<0.05) Effective (*P* <0.05)
Görgülü *et al.* 2011 (61)	CT	T1- Prior to RME T2- n/a T3- After 6m retention	Nasal cavity vol	T1-T3: 1419.47±647.69mm^3	12.1%	Effective (*P* <0.001)
Haralambidis *et al.* 2009 (63)	CT	T1- Prior to RME T2- n/a	Anterior nasal cavity vol	T1-T3: 5437.36±1097.13mm^3 vs 6045.7±1247.31mm^3	11.2%	Effective (*P*=0.0001)

		T3- After 3m retention				
Kabalan *et al.* 2015 (53)	AR(ND & D)	T1- Prior to RME T2- n/a T3- After 6m retention	Right nasal cavity vol 1 Right nasal cavity vol 2 Left nasal cavity vol 1 Left nasal cavity vol 2	T1-T3: -0.15 ± 1.64 cm^3 T1-T3: 1.1 ± 4.53 cm^3 T1-T3: 0.19 ± 1.69 cm^3 T1-T3: -0.26 ± 1.77 cm^3	n/a n/a n/a n/a	Not-effective (*P*>0.05) Not-effective (*P* >0.05) Not-effective (*P* >0.05) Not-effective (*P*>0.05)
Li *et al.*2015 (70)	CBCT	T1- Prior to RME T2- 16 days after complete RME expansion T3- After 4m retention	Nasopharyngeal volume Oropharyngeal volume	T1:3462±1147 mm^3 vs T2:4496±983 mm^3 T1:3462±1147 mm^3 vs T3:4437±896 mm^3 T1:7236±2398 mm^3 vs T2:7515±2362 mm^3 T1:7236±2398 mm^3 vs T3:7612±2078 mm^3	29.9% 28.2% n/a n/a	Effective (*P*<0.05) Effective (*P*<0.05) Not-effective (*P* n/a) Not-effective (*P* n/a)
Marini *et al.* 2007 (66)	Photogrammetry	T1- Prior to RME T2- n/a T3- After 3m retention	Palatal vol	T1-T3: n/a	2.3-8.5%	Effective (*P*<0.001)
Oliveira De Felippe *et al.* 2008 (64)	AR (ND) Model scanning	T1- Prior to RME T2- After complete expansion T3- After 4m retention	Nasal cavity vol R Nasal cavity vol L Nasal cavity vol Total Palatal vol	T1-T2: 7.58±2.72cm^3 vs 9.25±2.89 cm^3 T2-T3: 9.25±2.89 vs 9.19±2.39 cm^3 T1-T3: 7.58±2.72cm^3 vs 9.19±2.39 cm^3 T1-T3: 5100.01±1324.91mm^3 vs 6414.79±3167.49 mm^3	18% 17.5% 40.6% 25.8%	Effective (*P*=0.007) Not-Effective (*P*=0.265) Effective (*P*=0.000) Effective (*P*=0.000)
Palaisa *et al.* 2007 (65)	CT	T1- Prior to RME T2- After complete expansion T3- After 3m retention	Nasal cavity vol	T1-T2: 2.08±2.66 cm^3 T2-T3: 4.90±2.30 cm^3 T1-T3: 6.99±2.45 cm^3	10.7% 22.6% 35%	Effective (*P* <0.05) Effective (*P* <0.05) Effective (*P* <0.05)
Pangrazio-Kulbersh *et al.* 2012 (58)	CBCT	T1- Prior to RME T2- n/a T3- After 6m retention	Maxillary sinus vol Banded Bonded Posterior Airway vol Banded Bonded	 T1-T3: 21769.38 ± 6275.28 vs 24352.32 ± 6664.68 mm^3 T1-T3: 27674.75 ± 10404.67 vs 29412.09 ± 9782.13 mm^3 T1-T3: 11858.93 ± 3988.74 vs 19277.53 ± 17421.86 mm^3 T1-T3: 11518.73 ± 4742.75 vs 11423.56 ± 2544.65 mm^3	 11.8% 6.3% 63% -1%	Effective Banded (*P* <0.01) Bonded (*P* <0.01) Not-effective Banded (*P*=0.16) Bonded (*P*=0.93)
Ribeiro 2011 (71); Ribeiro *et al.* 2012 (57)	CBCT	T1- Prior to RME T2- n/a T3- After 4m retention	Nasopharynx Oropharynx	T1-T3: 879.77±2628.01mm^3 T1-T3: 239.36±532.99mm^3	11.5% 16.2%	Not-effective (*P*=0.11) Effective (*P*=0.05)
Smith *et al.* 2012 (56)	Spiral CT	T1- Prior to RME T2- n/a	Nasal cavity vol Nasopharynx vol	T1-T3: 3641±5545mm^3 T1-T3: 522±548mm^3	15.2% 16.2%	Effective (*P*=0.00) Effective (*P*=0.00)

		T3- After 3m retention	Oropharynx vol	T1-T3: 184±4335mm^3	-1.7%	Not-effective (*P*=0.11)
			Hypopharynx vol	T1-T3: 170±1021mm^3	5.1%	Not-effective (*P*=0.22)
			Right Mx sinus vol	T1-T3: 326±1898mm^3	2.6%	Not-effective (*P*=0.50)
			Left Mx sinus vol	T1-T3: 452±1825mm^3	3.7%	Not-effective (*P*=0.17)
Sökücü *et al.* 2010 (62)	AR (ND & D)	T1- Prior to RME T2- After complete expansion T3- After 6m retention	Nasal cavity volume	T1-T2 (ND): 0.172±0.042cm^3 vs 0.220±0.044 cm^3	28%	Effective (*P* <0.05)
				T1-T2 (D): 0.198±0.048cm^3 vs 0.266±0.047 cm^3	34.3%	Effective (*P* <0.05)
				T2-T3 (ND): 0.220±0.044cm^3 vs 0.205±0.043 cm^3	-6.8%	Effective (*P* <0.05)
				T2-T3 (D): 0.266±0.047cm^3 vs 0.242±0.041 cm^3	-9%	Effective (*P* <0.05)
				T1-T3 (ND): 0.172±0.042cm^3 vs 0.205±0.043 cm^3	19.1%	Effective (<*P* 0.05)
				T1-T3 (D): 0.198±0.048cm^3 vs 0.242±0.041 cm^3	22.2%	Effective (*P* <0.05)
Zeng & Gao 2013 (54)	CBCT	T1- Prior to RME T2- n/a T3- After 3m retention	Lower Nasal vol	T1-T3: 1348.5±640.1mm^3	8.2%	Effective (*P*=0.000)
			Nasopharyngeal vol	T1-T3: -178.7±884.7mm^3	-6.8%	Not-effective (*P*=0.447)
			Oropharyngeal vol	T1-T3: -1325.0±2232.7mm^3	-12.2	Effective (*P*=0.037)

*Calculated % value based on published data;

RME, rapid maxillary expansion; AR, acoustic rhinometry; ND, non decongested; D, decongested; CT, computed tomography; CBCT, cone beam computed tomography; Mx, maxillary; vol, volume; T1, time point prior to RME; T2, time point immediately after RME; T3, time point after retention; n/a, not available.

Supplementary Table 10. Expansion and Retention Protocols of Included Studies.

Study	Expander Design	Expansion Protocol	Expansion Period	Retention
Almuzian *et al.* 2016 (67)	Hyrax cast type (fully covered buccal buccal teeth form 1st molars to canines with occlusal holes to aid removal)	¼ turn (0.25mm) twice a day until overexpansion (palatal cusps of upper molars occluded with the buccal cusps of the lower molars)	Mean active expansion 14 days (range:12-21 days)	Not specified
Azaredo 2014 (68)	Hass or Hyrax (details not specified)	1mm (4 turns) immediately after appliance cementation followed by 0.5mm (2 turns) per day	Active expansion of 19 days (total expansion of 8mm)	Appliance left in place for 3 months after active expansion (doesn't state if it was fixed or not)
Babacan *et al.* 2006 (15)	Hyrax full coverage bonded	¼ turn per day until desired expansion achieved	Mean activation period 25.2 ± 3.82 days "until the desired suture opening was achieved"	Screw tied off with 0.014" ligature wire, Hyrax removed after 1 week to minimize discomfort. Cleaned and used as removal retainer for approximately 6 month retention period. Mean retention period 6.15 ± 0.17 months
Cappellette *et al.* 2008 (17)	Hyrax banded on U6s	6-8 turns on first day, then 2 turns per day thereafter until the complete maxillary expansion	Not stated, activated "until the complete maxillary expansion"	Appliance left in place for 3 months after active expansion (doesn't state if it was fixed or not)
Chang 2011 (69); Chang *et al.* 2013 (55)	Hyrax banded on U4s & U6s	One activation (90° turn) of jackscrew per day Clinical observation of 2-3mm of overexpansion marked the termination of expansion	28 consecutive days or until resolution of the posterior crossbite.	Hyrax left in place and tied off with a ligature wire as well as composite material
Cordasco *et al.* 2012 (60)	Hyrax banded to U6s only	Screw initially turned 8 times (1.6mm initial activation), then patients instructed to turn 3 times per day (0.6mm activation per day) until end-point	Expansion continued until mild over-correction of 2mm was achieved. Average active expansion period of 12.6 days	Hyrax locked with composite & removed 7months after it was inserted (approximately 6.5 months retention period)
Darsey *et al.* 2012 (59)	Hyrax banded either U6s only with arms, or U4s & U6s	2 turns per day	Expansion time: 3-4 weeks Mean expansion time: 22.3 days Until maxillary arch constriction was overcorrected (overcorrection amount not specified)	
Doruk *et al.* 2007 (16)	Hyrax full coverage bonded	Activate the screw (1/4 turn) twice a day for first week (0.5mm), then once	Mean active expansion:20.7 +/- 4.6 days	Retention protocol not described Mean retention period = 6 +/- 2.2 months

		per day thereafter (0.25mm)	Until the posterior crossbite was eliminated	
Görgülü *et al.* 2011 (61)	Hyrax bonded, acrylic occlusal coverage of 3mm from U4-U7	2 turns per day (approximately 0.25mm per turn) until end-point including standardized amount of overcorrection (not-specified)	Not specified "Amount of expansion was approximately 8mm at appliance screw"	Not specified
Haralambidis *et al.* 2009 (63)	Hyrax bonded acrylic cap splint	Hyrax activated twice by clinician at cementation, parent then activates screw 1/4 turn twice daily until end point.	Duration: 23.7± 5.5 days Expansion terminated just before reaching Bu cross-bite in all patients	Appliance screw secured with stainless steel ligature wire and left in place for 3 months, then soldered TPA with palatal arms extending along premolars. Follow-up records taken at appliance removal and then TPA placed right away
Kabalan *et al.* 2015 (53)	Hyrax banded on U4s & U6s	Activate expander 2 turns daily (0.5mm/day) until appropriate expansion	Not specified	Hyrax fixed with ligature wire, RME left in place for 6 months
Li *et al.*2015 (70)	Hyrax	Activate expander 2 turns daily (0.5mm/day)	Active expansion of 16 days	Hyrax screw secured with composite and appliance left in place for 3months after end of active expansion
Marini *et al.* 2007 (66)	Hyrax bonded splint expander	¼" turn (0.25mm) twice a day	Until maxillary molar palatal cusps contacted lower molar buccal cusps	RME left in place for 3months after end of activation
Oliveira De Felippe *et al.* 2008 (64)	Haas-banded hyrax - U4s & U6s with palatal acrylic pads Banded hyrax - U4s & U6s Bonded hyrax with occlusal capping splint	2 per day (50%) 1 per day (42%) 1 every other day (8%) Midline diastema formation was observed in 32 of 38 patients	Average active expansion: 40days (range: 14-173days). Clinical observation of 2-3mm of overexpansion When occlusal aspect of lingual cusp of maxillary first molar contacted the occlusal aspect of the facial cusp of mandibular first molars.	RME was fixed (not specified) and left in place for retention Average retention period:121days (range :94-183 days)
Palaisa *et al.* 2007 (65)	Hyrax bonded or banded	Not specified	Average activation of hyrax:6.1mm +/- 1.7mm	Not specified
Pangrazio-Kulbersh *et al.* 2012 (58)	Hyrax Banded to U6s with palatal wire, or	Not specified (calculated to be approximately 1 turn	Active expansion 4-6 weeks Activation amount 6-10mm	6 months retention details not provided

	Bonded acrylic cap coverage	per day)		
Ribeiro 2011 (71); Ribeiro *et al.* 2012 (57)	Hyrax bonded	Not specified	Not specified	4 months retention period details not provided
Smith *et al.* 2012 (56)	Hyrax banded either U4s & U6s, or UDs & U6s	Turn appliance 2 times twice daily (total 0.8mm activation per day) until end-point	Until palatal cusps of maxillary first permanent molars contacted the buccal cusps of the mandibular first molars	Exact method not described, assuming expander left in place for 3months Average period from last activation to final records 91 +/- 3.5days
Sökücü *et al.* 2010 (62)	Hyrax acrylic bonded full tooth & tissue borne	¼ turn twice per day	When occlusal aspect of U6 lingual cusp contacted the occlusal aspect of the L6 facial cusp Mean activation period 22.4 +/- 4.01days	Expansion screw fixed with 0.014" stainless steel ligature wire. Appliance left passive for 1 week to minimize discomfort at removal. Appliance removed, cleaned and used as a removable retention appliance. Mean retention period 6.2 +/- 0.16 months
Zeng & Gao 2013 (54)	Hyrax banded on U4s & U6s	Activated expander 2 turns per day until end-point	Activation period ranged 2-3weeks (2.7-6.3mm). When palatal cusp of U6s contacted Buccal cusps of L6s	Hyrax screw locked with composite and left in place for further 3m

U4s, upper first premolars; U6s, upper first molars; L6s, lower first molars; TPA, transpalatal arch.

Supplementary Table 11. Details on the composition of the main outcome (composite airway volume)

Study	Volumes included in composite airway volume
Almuzian *et al.* 2016 (67)	Left sinus/right sinus/lower nasal cavity/nasopharynx/upper velopharynx/lower velopharynx
Azeredo 2014 (68)	Oropharynx
Chang 2011 (69); Chang *et al.* 2013 (55)	Velopharynx/oropharynx
Cordasco *et al.* 2012 (60)	Total nasal cavity
Darsey *et al.* 2012 (59)	Total sinus
Doruk *et al.* 2007 (16)	Total nasal cavity
Gorgulu *et al.* 2011 (61)	Total nasal cavity
Haralambidis *et al.* 2009 (63)	Total nasal cavity
Li *et al.* 2015 (70)	Nasopharynx/oropharynx
Palaisa *et al.* 2007 (65)	Total nasal cavity
Pangrazio-Kulbersh *et al.* 2012 (58)	Total sinus/nasopharynx/velopharynx/oropharynx
Ribeiro 2011 (71); Ribeiro *et al.* 2012 (57)	Nasopharynx/oropharynx
Smith *et al.* 2012 (56)	Left sinus/right sinus/total nasal cavity/nasopharynx/hypopharynx/oropharynx
Zeng & Gao 2013 (54)	Total nasal cavity/nasopharynx/oropharynx

Supplementary Table 12. Results of the effect of rapid maxillary expansion on each separate volume (mm^3) originally reported in the treated groups of included studies.

Outcome	Measurement	Timing	Studies	Change (95% CI)	P	95% Predictive Interval	I^2 (95% interval)
Left S	CT	post-expansion	2	-75.51 (-19369.28,19218.25)	0.994	NA	0% (NA)
Left S	CT	post-retention	1	452.00 (-15544.54,16448.54)	0.956	NA	NA
Right S	CT	post-expansion	2	214.29 (-16458.42,16886.99)	0.980	NA	0% (NA)
Right S	CT	post-retention	1	326.00 (-16310.39,16962.39)	0.969	NA	NA
TS	CT	post-expansion	1	69.30 (-61183.71,61322.31)	0.998	NA	NA
TS	CT	post-retention	1	2215.29 (-119.91,4550.49)	0.063	NA	NA
Lower NC	CT	post-expansion	1	815.00 (-17422.27,19052.27)	0.930	NA	NA
Anterior NC	CT	post-retention	1	580.00 (-1249.39,2409.39)	0.534	NA	NA
Posterior NC	CT	post-retention	1	690.00 (-1194.84,2574.84)	0.473	NA	NA
Left NC	CT	post-expansion	1	1238.00 (-11132.68,13608.68)	0.844	NA	NA
Left NC	CT	post-retention	1	3671.00 (-8084.55,15426.55)	0.541	NA	NA
Left NC	AR-basal	post-expansion	1	445.45 (-191.58,1082.48)	0.171	NA	NA
Left NC	AR-basal	post-retention	1	751.32 (153.51,1349.13)	0.014	NA	NA
Left NC	AR-basal	post-retention (long-term)	1	1442.11 (844.30,2039.92)	0.000	NA	NA
Right NC	CT	post-expansion	1	838.00 (-10789.41,12465.41)	0.888	NA	NA
Right NC	CT	post-retention	1	3320.00 (-9076.30,15716.30)	0.600	NA	NA
Right NC	AR-basal	post-expansion	1	1001.96 (382.32,1621.60)	0.002	NA	NA
Right NC	AR-basal	post-retention	1	860.79 (279.70,1441.88)	0.004	NA	NA
Right NC	AR-basal	post-retention (long-term)	1	1632.37 (1051.28,2213.46)	<0.001	NA	NA
TNC	CT	post-expansion	1	2080.00 (-20645.13,24805.13)	0.858	NA	NA
TNC	CT	post-retention	7	1362.46 (-1755.02,3739.41)	0.261	-1755.02,4479.94	0% (0%,58%)
TNC	AR-basal	post-expansion	2	642.53 (-693.82,1978.87)	0.346	NA	86% (NA)
TNC	AR-basal	post-retention	4	53.62 (-79.43, 186.67)	0.430	-438.02,545.25	73% (0%,88%)
TNC	AR-basal	post-retention (long-term)	1	3075.26 (2136.36,4014.16)	<0.001	-	NA
TNC	AR-decongested	post-expansion	1	69.00 (46.58,91.42)	<0.001	-	NA
TNC	AR-decongested	post-retention	3	25.31 (3.69,46.92)	0.022	-114.82,165.44	0% (0%,73%)
PV	CT	post-retention	1	1314.78 (382.21,2247.35)	0.006	NA	NA
PV	CT	post-retention (long-term)	1	1414.48 (481.91,2347.05)	0.003	NA	NA

upper VP	CT	post-retention	1	-35.00 (-4545.15,4475.15)	0.988	NA	NA
lower VP	CT	post-expansion	1	-311.00 (-13145.69,12523.69)	0.962	NA	NA
VP	CT	post-retention	1	1201.20 (-20937.36,23339.76)	0.915	NA	NA
NP	CT	post-expansion	2	662.27 (-6443.84,7768.38)	0.855	NA	0% (NA)
NP	CT	post-retention	4	396.71 (-3234.57,4028.00)	0.830	-7574.94,8368.36	0% (0%,68%)
OP	CT	post-expansion	2	390.43 (4.58,776.27)	0.047	NA	0% (NA)
OP	CT	post-retention	4	70.72 (-399.76,541.20)	0.768	-1269.58,1411.03	53% (0%,81%)
HP	CT	post-retention	1	170.00 (-8779.29,9119.29)	0.970	NA	NA
NP+VP+OP	CT	post-retention	1	4151.74 (-620.01,8923.49)	0.088	NA	NA
VP+OP	CT	post-retention	1	1735.10 (-42052.95,45523.14)	0.938	NA	NA

CI, confidence interval; S, sinus; CT, computed tomography; NA, not applicable; TS, total (left+right) sinus; NC, nasal cavity; AR, acoustic rhinometry; TNC, total nasal cavity; PV, palatal vault; VP, velopharynx; NP, nasopharynx; OP, oropharynx; HP, hypopharynx.

Supplementary Table 13. Results of additional analyses performed, including subgroup analyses, meta-regressions and assessment of reporting bias with the Egger test.

		Composite airway volume; CT; post-retention			Total nasal cavity volume; CT; post-retention		
Factor	**SG**	**Studies**	**Change (95% CI)**	**P among SG**	**Studies**	**Change (95% CI)**	**P among SG**
Appliance design	Banded	6	1299.04 (484.23,2113.85)	0.726	3	1305.18 (-1616.49,4226.84)	0.986
	Bonded	5	1040.57 (433.15,1647.99)		3	1255.89 (-2912.13,5423.92)	
		Studies	**Coefficient (95% CI)**	**P**	**Studies**	**Coefficient (95% CI)**	**P**
Patient age		9	-53.54 (-387.05,279.98)	0.716	5	-16.55 (-2005.84,1972.74)	0.981
Male/female ratio		10	-408.10 (-2329.76,1513.55)	0.637	6	157.90 (-6842.81,7158.60)	0.953
Egger's test for reporting bias		11	0.77 (-0.83,2.36)	0.304	-	-	-
		Studies	**Change (95% CI)**	**P**		**Difference between SGs (95% CI)**	**P among SGs**
Sensitivity analysis	Prospective	9	1032.53 (518.72, 1546.50)	<0.001		-560.86 (-2139.51, 1017.79)	0.442
	Retrospective	2	2710.49 (-791.69, 6212.66)	0.129			

CT, computed tomography; SG, subgroup; CI, confidence interval.